Editorial

Exercise Intolerance in Heart Failure With
Preserved Ejection Fraction
What Does the Heart Have To Do With It?

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Heart failure (HF) occurs when the cardiac output is unable to meet the body’s needs without an elevated filling pressure.1,2 Thus, exercise intolerance is an important symptomatic manifestation of HF, including patients with HF and a preserved ejection fraction (HFpEF).3

Two similar studies in this issue of Circulation: Heart Failure have reached different conclusions on the importance of cardiac dysfunction in producing exercise intolerance in HFpEF.1,2 Both groups performed upright cardiopulmonary exercise testing with hemodynamic monitoring in patients with preserved ejection fraction, elevated pulmonary capillary wedge pressure (PCW), and exercise intolerance. Santos et al4 found that the major contributor to exercise disability was a limitation of cardiac output, indicating a cardiac cause. This finding is consistent with a similar study by Abudiab et al.1 In contrast, Dhakal et al5 found that a peripheral limitation was the most important cause of reduced aerobic capacity, whereas impaired cardiac output had less impact. This finding is consistent with 2 other studies that indirectly estimated oxygen extraction.1,6 The goal of this editorial was to put these studies in perspective and explore what they tell us about HFpEF.

The delivery of oxygen to contracting muscles is essential to perform aerobic exercise. Optimum oxygen delivery requires oxygenation of the blood in the lungs, normal oxygen carrying capacity of the blood, adequate cardiac output that is appropriately distributed to match regional demands, and adequate tissue extraction of oxygen from the blood. Normal adults can increase oxygen consumption (VO2) >6-fold during exercise by: (1) increasing cardiac output because of a faster heart rate and enhanced stroke volume, and (2) augmenting oxygen extraction producing a fall in mixed venous oxygen content, thereby increasing the difference between arterial and venous oxygen content (CaO2−CVO2). Measuring VO2 during exercise provides a powerful method to objectively assess the degree of functional limitation and prognosis in patients with HF and a reduced ejection fraction. The study by Dhakal et al5 confirms that the cause of the reduction in peak VO2 in patients with HF and a reduced ejection fraction is predominantly (but not exclusively) because of an inadequate increase in cardiac output during exercise.

Santos et al4 studied patients with a reduced exercise capacity and an elevation of PCW during exercise (>20 mmHg) in subjects with normal ejection fraction. Interestingly, the majority of their patients did not have a PCW >15 mmHg at rest and would not have been included in the study by Dhakal et al.1 It is likely that a marked increase in PCW during exercise is because of a failure to augment left ventricular relaxation and reduce early diastolic left ventricular pressure.1,8–11 At peak exercise, the patients with HFpEF in this study had lower VO2 because of a reduced cardiac output, resulting from both impaired chronotropic response and reduced exercise stroke volume. The CaO2−CVO2 difference was not different in patients with HFpEF compared with that in the controls.

In a similar study, Abudiab et al1 studied 109 patients with HFpEF. Importantly, their patients’ resting PCW was elevated and increased during exercise along with the pulmonary artery pressure. Consistent with the study by Santos et al,4 the reduction in VO2 in patients with HFpEF was because of an inadequate increase in cardiac output, attributable to both lower stroke volume and heart rate at peak exercise. There was no difference in peak CaO2−CVO2. In fact, CaO2−CVO2 at matched workload was greater in HFpEF than that in controls.4

These concordant results from 2 large, carefully performed studies demonstrate that there are patients with HFpEF whose exercise intolerance is caused by failure to sufficiently augment cardiac output, without abnormalities in peripheral oxygen extraction.1,4 In these patients, the predominant mechanism limiting exercise capacity is cardiac, as is seen in most patients with HF and a reduced ejection fraction.

In contrast, Dhakal et al5 came to a different conclusion. They studied 48 patients with a history of HF, preserved ejection fraction, and a resting PCW >15 mmHg. The peak exercise CaO2−CVO2 was reduced in HFpEF compared with that in controls and in patients with HF and a reduced ejection fraction. In 40% of the patients with HFpEF, failure of CaO2−CVO2 to increase was the predominant factor limiting peak VO2 during exercise. Although this points to a failure of CVO2 decrease because of peripheral abnormalities, a cardiac limitation was also present. As a group, the exercise cardiac output was decreased in HFpEF compared with that in normal controls, attributable to both lower heart rate and stroke volume effects, in agreement with the studies of Santos et al4 and Abudiab et al.1 Furthermore, in the majority of patients, the reduction in cardiac output was a major contributor to the reduced VO2.5

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Similar to the findings of Dhakal et al, Haykowsky et al found that a failure of an indirect measure of CaO₂-CVO₂ to increase was the strongest correlate of low VO₂ in patients with a clinical diagnosis of HFpEF. In this study, peak cardiac output was reduced because of chronotropic incompetence in patients with HFpEF. In another noninvasive study, Bhella et al observed the same failure to increase estimated CaO₂-CVO₂ in patients with HFpEF.

Why does a failure to adequately increase CaO₂-CVO₂ contribute to exercise intolerance in some patients considered to have HFpEF but not others? First, it is possible that HF has been misdiagnosed or was not the cause of the exercise intolerance. However, in the study by Dhakal et al, there was direct measure of elevated PCW. Second, patients with HFpEF are commonly deconditioned and have comorbid conditions (including pulmonary disease) that may contribute to exercise intolerance, independent of the heart. Third, submaximal effort could also contribute to lower CaO₂-CVO₂ if patients stopped earlier than controls because of dyspnea caused by high PCW. However, Dhakal et al observed similar respiratory exchange ratio at peak exercise, suggesting equivalent effort despite reduced lactate levels.

The CaO₂-CVO₂ difference is not a direct measure of oxygen extraction by the muscles, as it also reflects the distribution of the cardiac output, both at the micro- and macrovascular beds. For example, at rest 50% of cardiac output is distributed to the kidneys, liver, and splanchnic circulations, where there is low oxygen extraction (local CaO₂-CVO₂ values of 1.2–4.0 mL/dL). During exercise, the proportion of flow distributed to these beds decreases relative to flow to the working muscles because of splanchnic and renal vasoconstriction and peripheral vasodilatation. In fact, in the absence of this regional vasoconstriction, humans would become hypotensive during exercise because increases in cardiac output would be preferentially routed through the lower impedance visceral circulations instead of working muscles.

Interestingly, Dhakal et al found that the failure of CVO₂ to fall during exercise was related to a greater increase in blood pressure during exercise. This may have been because of a failure of vasodilation in the muscles, preventing appropriate distribution of blood flow. Consistent with this concept, blunting marked exertional hypertension can improve exercise capacity. Conversely, one cannot exclude the possibility that inadequate regional vasoconstriction to nonskeletal muscle beds might also have contributed to the higher CVO₂. Indeed, the degree of splanchnic vasoconstriction during exercise is directly correlated with heart rate, which was lower in patients with HFpEF than in controls.

An abnormal distribution of cardiac output might also develop in HFpEF because of changes in lung mechanics. Elevations in PCW acutely increase lung water during exercise, reducing lung compliance, impairing ventilatory efficiency, and increasing the work of breathing. For example, mechanically unloading the diaphragm during exercise in HF patients (but not controls) improves peripheral blood flow during exercise. This suggests that increased work of breathing from pulmonary congestion in HF may shunt blood away from the locomotor muscles to perfuse the diaphragm and accessory muscles of breathing. This may then limit the ability of the muscles to reach maximal oxygen extraction, contributing to a failure to reduce CVO₂.

If impaired muscle extraction of O₂ contributes to the reduced exercise capacity of some patients with HFpEF, this may open new doors for treatment. For example, inorganic nitrates can improve vascular conductance and oxygen delivery to skeletal muscle during exercise. An alternative approach might be to modify the allosteric regulation of hemoglobin to allow for greater oxygen dissociation in the muscle. In addition, training may enhance exercise tolerance in HFpEF without producing an improvement in systolic or diastolic function. It may be that exercise testing can be used to identify the primary mechanisms of exercise intolerance in the individual patient, potentially allowing for more tailored therapies in HFpEF.

The analyses and interpretations from both studies are based on the assumption that increasing peak VO₂ should be the ultimate goal of treatment in HFpEF. However, most of the activities of daily living (where patients are symptomatic) fall far below peak VO₂, so efforts focused exclusively on maximal oxygen delivery and extraction may be less relevant in this range. Future study into the mechanisms of exercise intolerance during submaximal exercise may identify ways to improve everyday quality of life for patients with HFpEF.

All the studies on exercise considered here found that an inadequate increase in heart rate contributed to exercise intolerance in HFpEF. This was most apparent in patients who were treated with β-blockers. Because these agents have not been proven to improve survival in HFpEF, it may be advisable to avoid β-blockers in patients with HFpEF and exercise intolerance. In addition, a study on rate-adaptive atrial pacing in HFpEF is currently underway (NCT02145351).

In conclusion, the major reason for exercise intolerance in many patients with HFpEF is cardiac. These patients have markedly abnormal increases in PCW during exercise and inadequate increases in cardiac output. There are also patients with HFpEF in whom a failure to adequately reduce CVO₂ during exercise is an important contributor to exercise intolerance. It is possible that better evaluation of patients with HFpEF to differentiate mechanisms of exercise intolerance will point to new and effective treatments.

Disclosures

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References


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